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Title:

ANTAGONISM OF LYSERGIC ACID DIETHYLAMIDE (LSD)-INDUCED HYPERTHERMIA

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Antagonism of Lysergic Acid Diethylamide (LSD)-Induced Hyperthermia

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Introduction

The pyretogenic response to LSD has been reported by several workers and the influence of several drugs upon this phenomenon has been determined (Horita and Dille, 1954; Horita and Gogerty, 1958; Stahelin and Taeschler, 1959; Gogerty et al., 1957). The study by Horita and Gogerty (1958) indicated that the levels of serotonin (5-HT) are important to the pyretogenic response and that the response may be due to the indole character of LSD mimicking that of 5-HT. Horita (unpublished experiments) has also obtained pyretogenic responses by means of the administration of 3-, 4-dihydroxyphenylalanine (DOPA) in the presence of a monoamine oxidase (MAO) inhibitor.

In a study of the effects of various pharmacologic agents upon the LSD-induced behavioral changes in cats, Elder and Dille (in press) found that chlorpromazine (CPZ) and phenoxybenzamine (DBZ) produced the most significant changes in the reaction. From these studies it was inferred that DBZ might have an action upon the CNS which is not necessarily related to its adrenergic blocking effect.

Method

Male albino rabbits weighing from 1.2 to 2.0 kg were used throughout the study. The animals were housed two to a cage and allowed free access to food and water at all times. Each animal was used only once.

Rectal temperatures were taken with a Tri-R electronic thermometer every 30 minutes for 2 hours before the administration of any drug and for 5 hours after the administration of LSD. In those animals on a pretreatment schedule, control temperatures were determined prior to treatment and again before the LSD was given. Only those rabbits having a control temperature of 39° to 40° C before receiving any drug were used in this study. Room temperature was maintained at 25° ± 2° C.

LSD was used in doses of 50 µg/kg i.v. Reserpine, 2 mg/kg i.v., was given either immediately before or 24 hours before LSD. Guanethidine, 10 mg/kg i.v., was given either immediately before or 18.5 hours before LSD. Hexamethonium (C-6), 10 mg/kg i.v., was given 30 minutes before LSD and DBZ, 10 mg/kg i.v., was given either one hour or 23 hours before LSD.

The data from these experiments were examined for each point in time by the use of the t test, using the actual temperatures in all cases. Difference scores were used as a supplementary test in the case of reserpine pretreatment, since the control group receiving this drug immediately before LSD showed temperature responses which differed significantly from controls receiving no drug. Each experimental group contained from 5 to 8 rabbits except the LSD control group which consisted of 17 animals.

Results

Reserpine

It has been reported by Gogerty et al. (1957) that the effect of reserpine upon the pyretogenic response to LSD is dependent upon the relative times of administration of the two drugs. Reserpine given immediately before the administration of LSD appeared to potentiate

the response, while 22 to 24 hour pretreatment with reserpine attenuated the response.

Figure 1 shows the highly significant rise in temperature produced by reserpine given immediately before LSD in comparison to the LSD control response. It also shows that reserpine alone caused a significant rise in temperature from control levels. If these curves be examined by the use of difference scores obtained by subtracting out the reserpine control temperatures from the reserpine-LSD temperatures, and comparing the rise in temperature at each point in time for this group with the rises seen in the LSD control group, the only significant difference occurs at the 1.0 hour period and the LSD control response is the greater. In Figure 2 can be seen the antagonism of the LSD response produced by reserpine given 24 hours prior to LSD. This attenuation was highly significant from the 0.5 hour to the 4.5 hour period inclusive and was not associated with the slightly lower beginning temperature in these animals.

Guanethidine

This drug also produced a significant reduction in the pyretogenic response to LSD, but differed from reserpine in antagonizing the response whether given immediately before or 18.5 hours before LSD. The 18.5 hour pretreatment schedule produced a significant reduction in the response from the 0.5 to the 3.5 hour period inclusive, while in the group treated immediately before LSD this attenuation existed only from the 1.0 to the 2.0 hour period inclusive. Figures 3 and 4 show these responses.

Hexamethonium

Since reserpine and guanethidine were effective antagonists of LSD, it was thought that interruption of sympathetic outflow might be

responsible for this effect. However, C-6 failed completely as an antagonist to this response. Figure 5 shows that those rabbits treated with C-6 responded to LSD in a manner identical to the LSD control animals. Similar results were obtained with the use of pentolinium, 5.0 mg/kg i.v., 30 minutes before LSD.

Phenoxybenzamine

Administration of DBZ one hour before LSD completely prevented the response to LSD as shown in Figure 6. In those rabbits treated with DBZ 23 hours prior to LSD the antagonism was not so complete, but the response was reduced significantly in the 1.0 to 2.0 hour periods as shown in Figure 7.

Discussion

The hyperglycemic response to LSD is antagonized effectively by the administration of C-6 according to Konzett (1956), and hence would appear to be dependent upon intact sympathetic pathway. Since the pyretogenic response was not changed by C-6, intact sympathetic pathways appear to be unnecessary to this response. Both guanethidine and DBZ on the long pretreatment schedule produced some attenuation of the response, but only in the period of the maximal rise. Reserpine on the long pretreatment schedule and DBZ on the short pretreatment produced by far the most significant changes for the longest time.

Since Horita and Gogerty (1958) have shown that cross tolerance exists between the hyperthermic effects of the 5-HTP-MAO inhibitor combination and LSD, it would appear that 5-HT levels are intimately concerned with this response, or that LSD exerts its effect by mimicking the indole character of 5-HT. If this latter case be true, then reserpine, by releasing stored 5-HT, should either reinforce or antagonize

the LSD response depending upon the relative times of administration of the two drugs. Our results indicate such to be the case. This would imply that LSD and 5-HT act upon the same or similar sites to produce hyperthermia.

The effects in rabbits treated with reserpine might also be considered as due to the depletion of peripheral catechol amines, thereby preventing peripheral vasoconstriction. However, the results with guanethidine tend to cast some doubt upon this interpretation since the antagonism was neither as complete nor as long lasting with this material. The fact that this material caused only attenuation of the response militates against peripheral catechol amine release as the means by which reserpine intensified the LSD response. The apparent increase in response in the rabbits given reserpine immediately before LSD was very likely due to an increase in metabolic rate (Johnson and Sellers, 1961).

Several authors (Wells and Rall, 1949; Pinkston, 1935) have shown that interference with sympathetic discharge did not prevent hyperthermia produced by pyrogen, but did produce a reduction in the response. We would tend to agree with these findings on the basis of our experiments with reserpine, guanethidine and DBZ on the 23 hour pretreatment schedule.

It has been shown that DBZ and some of its congeners are effective antagonists of 5-HT in peripheral tissue (Caddum and Picarelli, 1957, Vane, 1957; Fingl and Gaddum, 1953; Erspamer, 1953), and it is possible that DBZ exerts some inhibitory effect upon the action of 5-HT in the central nervous system. Another possibility extends from the findings of Sréter and Friedman (1961) that DBZ interferes with skeletal muscle contraction. This could be interpreted as leading to a decrease in heat

production. Experiments designed to elucidate the mechanism of DBZ antagonism to LSD are now in progress.

Summary

The pyretogenic response to LSD was prevented by 30-minute pretreatment with DBZ. Reserpine given 24 hours before LSD and guanethidine 18.5 hours prior to LSD produced the most effective attenuation of the response. Reserpine given immediately before LSD caused an increased response to LSD, probably by increasing the metabolic rate. Hexamethonium had no effect upon the LSD response.

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Legends for Figures

Figure 1

Reserpine-LSD. Reserpine, 2.0 mg/kg I.v., given immediately before LSD, 50 µg/kg I.v., caused an apparent increase in the response to LSD. The responses to LSD were significantly different during the time periods between the arrows. When these data were examined by the use of difference scores obtained by subtracting the responses in the reserpine controls from the experimental group, no significant differences could be shown between the reserpine-LSD and the LSD groups. The digits in parentheses indicate the number of animals used.

Figure 2

Reserpine-LSD. Reserpine, 2.0 mg/kg I.v., 24 hours before LSD, 50 µg/kg I.v., produced a significant reduction in the pyretogenic response during the time periods between the arrows. The digits in parentheses indicate the number of animals used.

Figure 3

Guanethidine-LSD. Guanethidine, 10 mg/kg I.v., 18.5 hours prior to LSD, 50 µg/kg I.v., produced significant attenuation of the LSD response during the time periods between the arrows. The digits in parentheses indicate the number of animals.

Figure 4

Guanethidine-LSD. Guanethidine, 10 mg/kg I.v., immediately before LSD, 50 µg/kg I.v., reduced the peak response to LSD. The responses to LSD were significantly different during the time periods between the arrows. The digits in parentheses indicate the number of animals used.

Figure 5

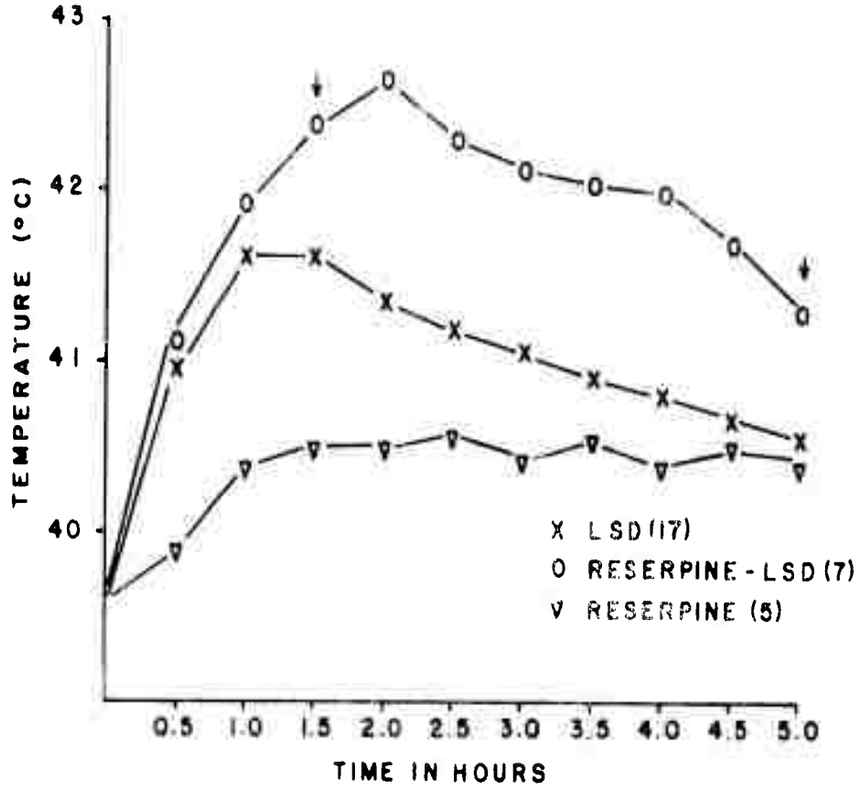
Hexamethonium-LSD. The response to LSD in animals treated with hexamethonium, 10 mg/kg I.v., 30 minutes before LSD, was the same as that in the LSD controls. The digits in parentheses indicate the number of animals used.

Figure 6

Phenoxybenzamine-LSD. Administration of DBZ, 10 mg/kg I.v., 60 minutes before LSD, prevented the pyretogenic response to LSD. $P < 0.01$ for all points in time. The digits in parentheses indicate the number of animals used.

Figure 7

Phenoxybenzamine-LSD. DBZ, 10 mg/kg I.v., 23 hours before LSD, reduced the peak response to LSD. The responses to LSD were significantly different during the time periods between the arrows. The digits in parentheses indicate the number of animals used.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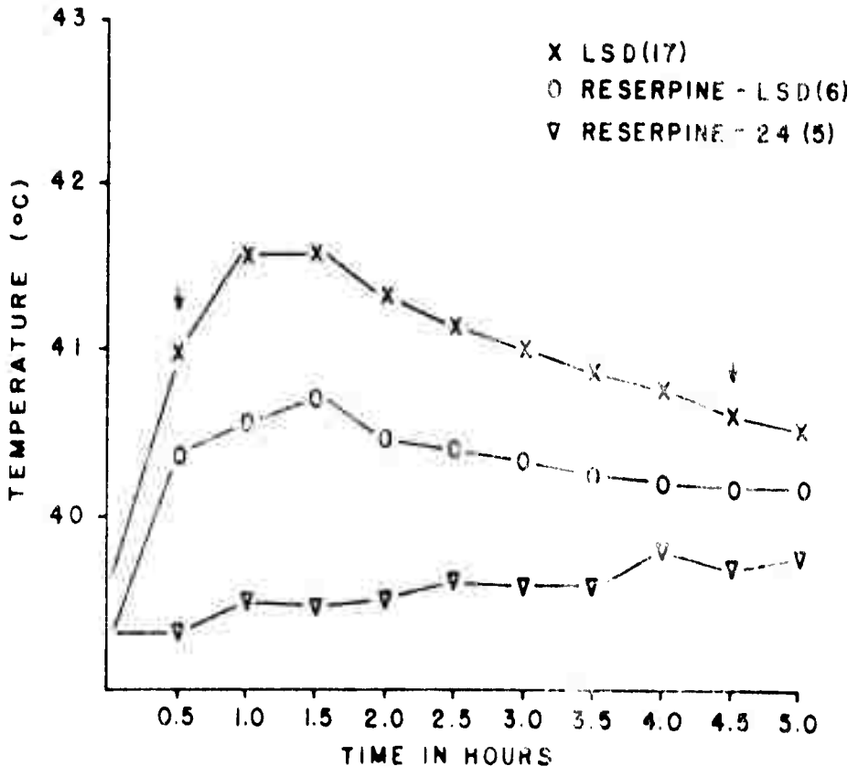
42
41
40
TEMPERATURE (°C)
X LSD(17)
O RESERPINE - LSD(7)
V RESERPINE (5)
0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0
TIME IN HOURS

Figure 1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TEMPERATURE (°C)
X LSD(17)
O RESERPINE - LSD(6)
V RESERPINE - 24 (5)
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TIME IN HOURS

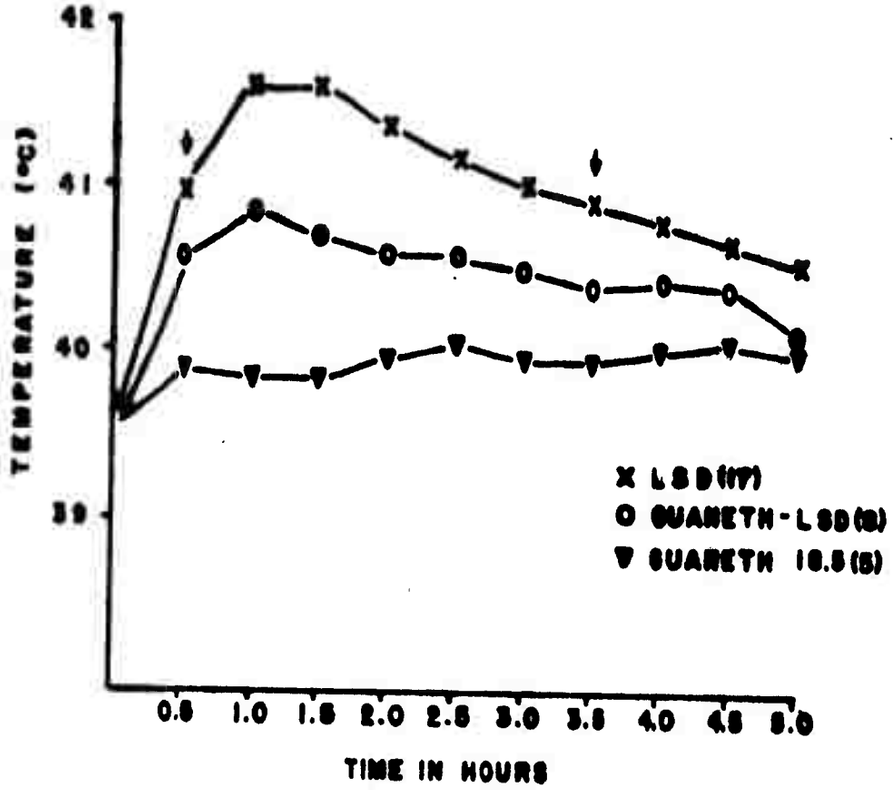


Figure 3

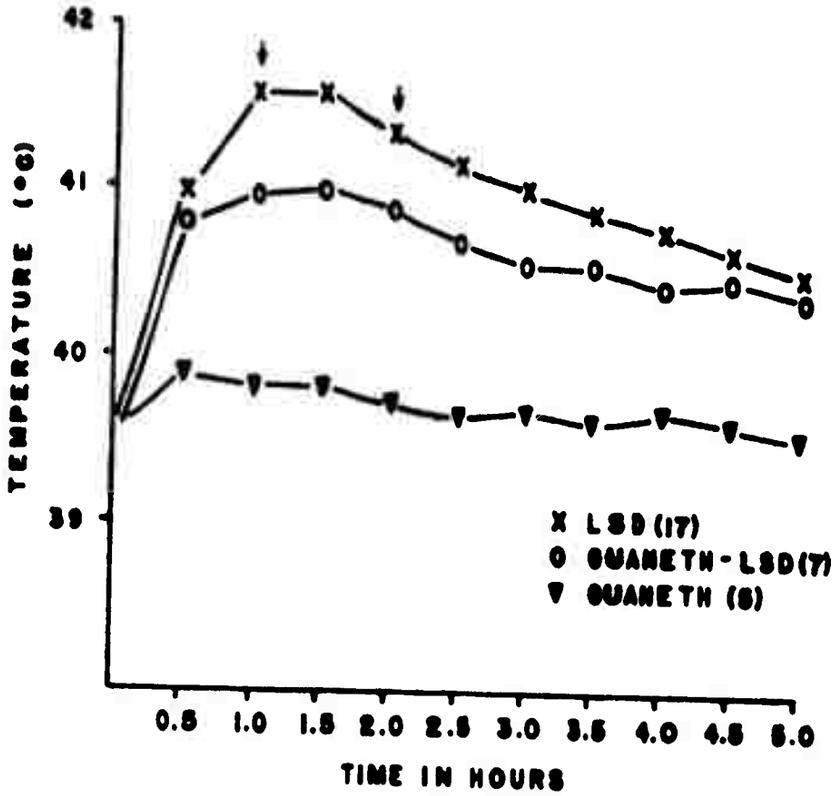


Figure 4

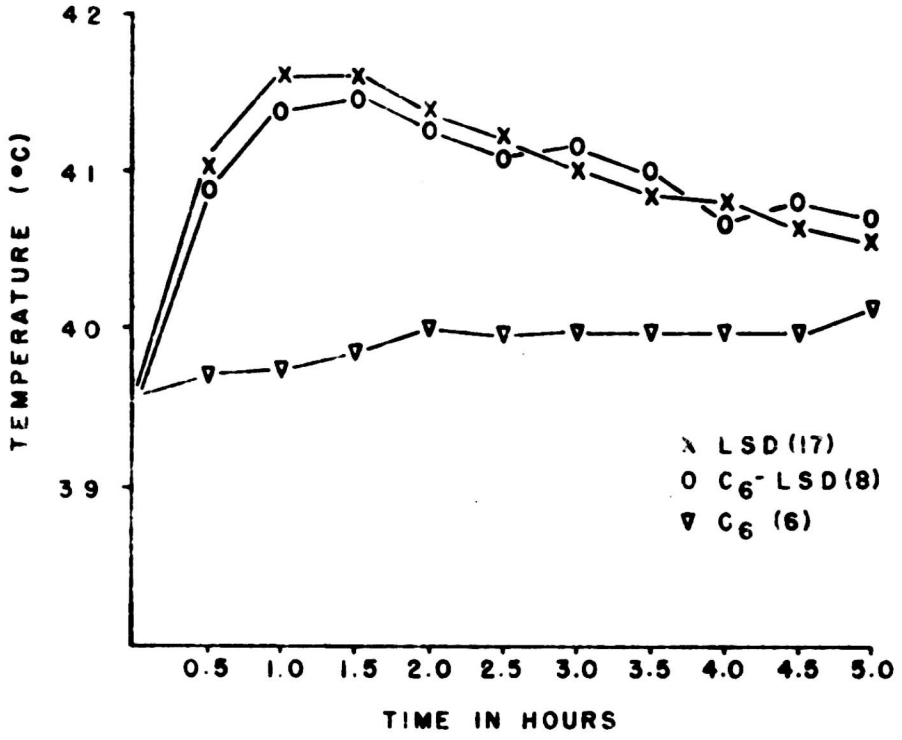


Figure 5

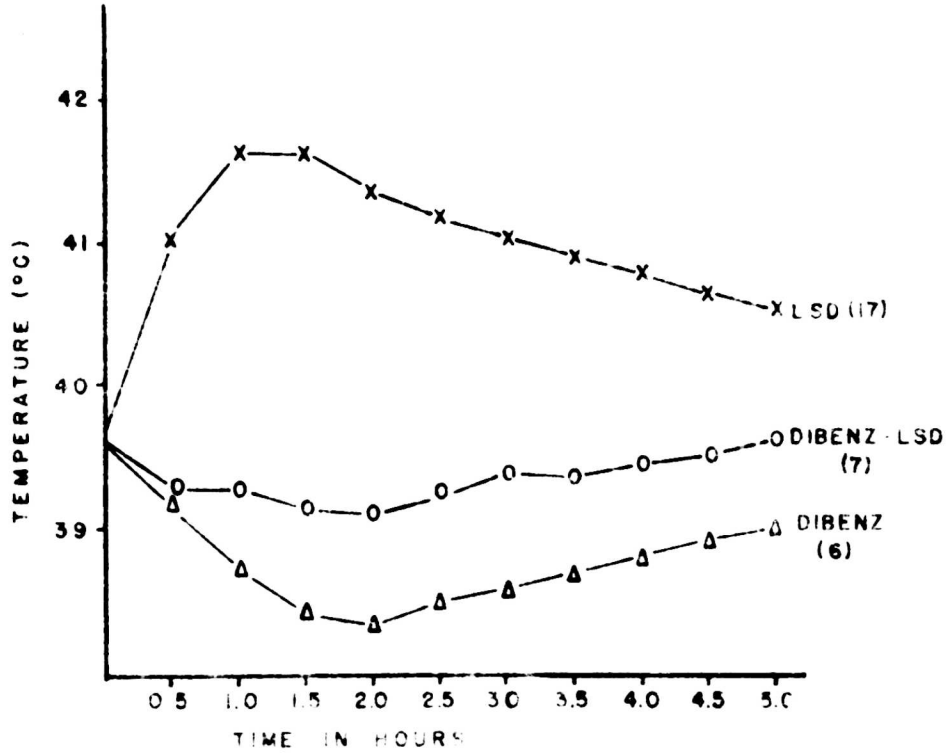
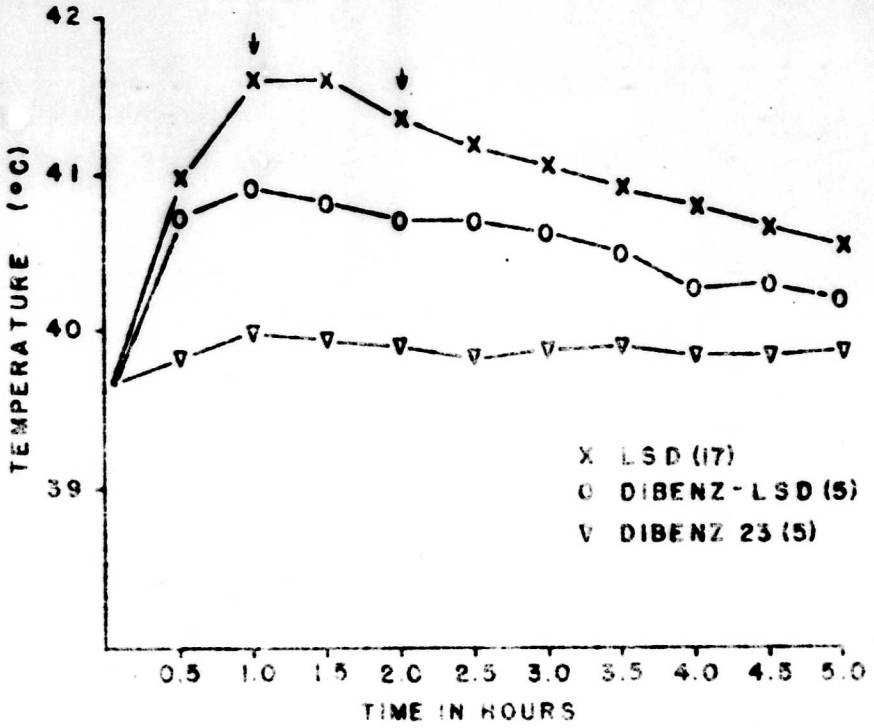


Figure 6


42
41
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TEMPERATURE (°C)
X LSD (17)
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V DIBENZ 23 (5)
0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0
TIME IN HOURS

Figure 7

UNCLASSIFIED